UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,853	09/24/2003	Dinah W. Y. Sah	A118 US	4306

26168 7590 01/09/2007
FISH & RICHARDSON
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,853	SAH, DINAH W. Y.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,10-12,27-38 and 57-70* is/are pending in the application.

4a) Of the above claim(s) *27-34 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,10-12,35-37 and 57-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/24/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/27/05,7/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/ Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on October 10, 2006 is acknowledged.

Claims 1, 2, 4, 5, 10-12, 27-38, 57-70 are pending. Claims 27-34 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 10, 2006. Claims 1, 2, 4, 5, 10-12, 35-37, 57-70 are under examination in this office action in light of diabetic neuropathy.

Information Disclosure Statement

The information disclosure statement filed November 27, 2006 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement, such as a form of PTO-1449. The information disclosure

statement has been placed in the application file, but the information referred to therein has not been considered.

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

Claim 2 is objected to as encompassing non-elected diseases.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 10-12, 35-37, 57-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving the behavior tests on a mouse model of tactile allodynia and thermal hyperalgesia (Chung L5/L6 spinal nerve ligation (SNL) model) and a mouse model of diabetic neuropathy induced by streptozotocin (STZ) by administering SEQ ID NO:2 or a polypeptide consisting of aa 28-140 of SEQ ID NO:2 (NBN113) to the test mice, does not reasonably provide enablement for a method of treating all neuropathic pains in a subject comprising administering all neublastin polypeptides to the subject as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1, 2, 4, 5, 10-12, 35-37, 57-70 are directed to a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neublastin polypeptide wherein the neuropathic pain is associated with diabetic neuropathy including allodynia and hyperalgesic pain. Claims 66-70 recite the neublastin polypeptide comprising an amino acid sequence at least 85%-95% identical to aa 28-140 of SEQ ID NO:2 or a neublastin polypeptide comprising amino acids 42-140 or 37-140 of SEQ ID NO:2.

The nature of the instant invention is based on the findings that administration of SEQ ID NO:2 or aa 28-140 of SEQ ID NO:2 (NBN113) to a mouse model of tactile allodynia and thermal hyperalgesia (Chung L5/L6 spinal nerve ligation (SNL) model) and a mouse model of diabetic neuropathy induced by streptozotocin (STZ) can improve their behavior tests on tactile and thermal response and paw withdrawal latency respectively. Applicant describes that administering SEQ ID NO:2 or aa 28-140 of SEQ ID NO:2 (NBN113) into mice of the SNL model can improve the Von Frey and

Hargreave's behavior tests in tactile and thermal responses, respectively. In addition, administering NBN113 can also improve paw withdrawal latency in the STZ model of diabetic neuropathy.

Based on the prior art and the specification, Applicant is enabled for administration SEQ ID NO:2 or a polypeptide consisting of aa 28-140 of SEQ ID NO:2 (NBN 113) to reduce the neuropathic pain due to tactile allodynia or thermal hyperalgesia caused by diabetes neuropathy. However, the claims are not limited to reducing the neuropathic pain caused by diabetes neuropathy. It is known in the art that neuropathic pain can be due to direct peripheral nerve damage, the toxic side effects of drugs, diseases such as diabetes or HIV-infection or any combination of these factors (see p. 834, White et al. Nat Rev. Drug discovery. 2005. 4: 834-844). The inflammation response caused by peripheral nerve damages or infection is complex. The immune defensive mechanisms and recruitment of leukocytes and healing system is accompanied with pain and produces a cascade of cellular events in the peripheral nervous system (PNS). They include the activation of different cell types such as glial cells in peripheral nerve/dorsal root ganglia, a neuroinflammatory response with the release of chemical mediators including several proinflammatory cytokines/chemokines including TNFα and IL-1β and increased neuronal excitability. The animal models for neuropathic pain cannot fully reflect the complexity of diabetic neuropathic pain or other neuropathic pains in humans. In addition, each animal model of specific neuropathic pain can be only interpreted partially and specifically (p. 957, conclusions. Wang et al. Adv. Drug Delivery Rev. 2003. 55:949-965). Applicant is enabled for improving the

behaviors associated with tactile allodynia and thermal hyperalgesia in SNL mouse model and improve the behavior associated with pain in STZ mouse model of diabetic neuropathy based on the working examples in the specification, as originally filed. However, the instant specification, as filed, provides insufficient guidance as to enable one skilled in the art to practice the full scope of the invention since neuropathic pain could be caused by other different mechanisms such as viral infection or phantom pain, which has no clear cause to induce neuropathic pain.

For example, it has been shown that neuropathic pain caused by HIV-infection could be due to multiple factors including the production of chemokines of infected macrophage/microglial cells responsive to infection or the damages caused by the binding of the viral coat protein gp120 to both neuronal and non-neuronal CCR5 and CXCR4 receptors in the PNS and CNS, which triggers signaling for diverse neuropathies (see p. p. 640, White et al. Nat Rev. Drug discovery. 2005. 4: 834-844). The neuropathic pain induced by HIV can also be complicated and synergistic by highly active anti-reroviral treatment (HAART) such as zidovudine (AZT) and didanosine (ddI). The treatment of HARRT induces inflammatory demyelinating polyneuorpathy and progressive polyradiculopathy and could be due to a metabolic toxicity and cytomegalovirus infection. Since the cause of neuropathic pain induced by HIV-infection is not quite understood and the neuronal damages caused by the treatment of anti-HIV are irreversible, it is unpredictable whether administering any neublastin polypeptide or neublastin polypeptide comprising homologues at least 85%-95% identical to aa 28-140 of SEQ ID NO:2 or a neublastin polypeptide comprising aa 42-140 or 37-140 of SEQ ID

NO:2 could treat neuropathic pain caused by HIV-infection or anti-HIV treatment. Thus, it is unpredictable whether all neublastin polypeptides could be used to treat all forms of neuropathic pains that could be caused by diverse mechanisms.

In addition, the claims are not limited to using the full length of SEQ ID NO:2 or a polypeptide consisting of aa 28-140 of SEQ ID NO:2. Applicant fails to provide sufficient guidance as to what specific conserved structures/characteristics are required for all neublastin polypeptides or neublastin polypeptides comprising homologues at least 85%-95% identical to aa 28-140 of SEQ ID NO:2 in order to maintain the claimed activity in treating certain types of neuropathic pains. Applicant also fails to show that whether a neublastin polypeptide comprising 42-140 or 37-140 of SEQ ID NO:2 would also have the same effect as a polypeptide consisting of aa 28-140 of SEQ ID NO:2. It has been shown that a single amino acid change can alter the function of a protein. For example, a substitution of lysine residue by glutamic acid at position 118 of acidic fibroblast growth factor results in a substantial loss of its biological activity including the binding ability to heparin and its receptor (Burgess et al. J of Cell Bio. 111:2129-2138, 1990). It has also been shown that different homologs of receptors even binding to the same ligand may function differently for example the estrogen receptor. Both estrogen receptor-α and -β bind to estrogen and share significant homology (95% amino acid identity for DNA-binding domain and 55% amino acid identity for ligand-binding domain). However, estrogen receptor-β functions as a dominant negative molecule in cell proliferation whereas estrogen receptor-α functions in promoting cell proliferation. See Gustafsson, J. A.. Eur J Cancer. 2000 Sep;36 Suppl 4:S16. In addition to a core

determinant sequence, the protein-protein interaction also relies on the flanking or noncontiguous residues (see p. 445 the second column, first paragraph, Pawson et al. 2003, Science 300:445-452). The optimal binding motif for a domain is not necessarily suitable for physiological or in vivo interaction. The predictive data always need to be validated by actual analyses in cells (see p. 445, the third column, second paragraph, Pawson et al. 2003, Science 300:445-452). Although Applicant describe several examples on p. 8-13, Applicant fails to disclose the common conserved functional structures/characteristics that are required for these neublastin polypeptides comprising homologues with limited homology to aa 28-140 of SEQ ID NO:2. Applicant fails to teach what amino acids could be/could not be changed in order to maintain the claimed activity of the disclosed protein. A skilled artisan cannot predict the function/activity of these claimed homologues. Applicant fails to provide sufficient guidance as to whether other neublastin polypeptides comprising aa 37-140 or 42-140 of SEQ ID NO:2 or homologues with limited homology to aa 28-140 of SEQ ID NO:2 could actually improve the animal models used in the specification or other forms of neuropathic pain caused by different mechanisms since the structure- functional relationship of these claimed polypeptides with the claimed invention is unknown. Applicant provides insufficient guidance as to enable one of skill in the art to practice the full scope of invention without undue experimentation. Thus it is unpredictable whether these claimed neublastin polypeptides and neublastin polypeptides comprising homologues having 85%-95% identity of aa 28-140 of SEQ ID NO:2 could actually maintain the claimed activity as in

SEQ ID NO:2 or a polypeptide consisting of aa 28-140 of SEQ ID NO:2 , indicating that undue experimentation is required to practice the claimed invention.

Therefore, in view of the breadth of the claims, the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neublastin polypeptide wherein the neuropathic pain is associated with diabetic neuropathy including allodynia and hyperalgesic pain and wherein the neublastin polypeptide could be any neublastin polypeptide or a neublastin polypeptide comprising an amino acid sequence at least 85%-95% identical to amino acids 28-140 of SEQ ID NO:2 or amino acids 42-140 of SEQ ID NO:2 or amino acids 37-140 of SEQ ID NO:2.

Claims 1, 2, 4, 5, 10-12, 35-37, 57-68 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial

structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 1, 2, 4, 5, 10-12, 35-37, 57-68 are directed to a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neublastin polypeptide wherein the neuropathic pain is associated with diabetic neuropathy including allodynia and hyperalgesic pain and wherein the neublastin polypeptide could be any neublastin polypeptide or a polypeptide comprising an amino acid sequence at least 85%-95% identical to amino acids 28-140 of SEQ ID NO:2 or amino acids 42-140 of SEQ ID NO:2 or amino acids 37-140 of SEQ ID NO:2. The claims 1, 2, 4, 5, 10-12, 35-37, 57-65 do not require that a neublastin polypeptide used in the claimed methods as recited in claim 1 possess any particular biological activity, any particular conserved structure, or other disclosed distinguishing feature. Although claims 66-68 recite neurotrophic activity, Applicant fails to describe/specify what specific common structures/features that are required for maintaining the activity as in SEQ ID NO:2 or aa 28-140 of SEQ ID NO:2. Thus, claim 1 encompasses a genus of neublastin polypeptides and claims 66-68 encompass a genus of neublastin polypeptides that are defined only by sequence similarity. However, the instant specification fails to describe the entire genus of neublastin polypeptides that could be used in the claimed method. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what

Applicant is claiming. From the specification, it is clear that Applicant is in possession of SEQ ID NO:2 and a neublastin polypeptide consisting of aa 28-140 of SEQ ID NO:2 that can be used in the claimed method. However, the claims are not limited to the full length protein of SEQ ID NO:2 or a polypeptide consisting of aa 28-140 of SEQ ID NO:2. Claim 1 recites a neublastin polypeptide and claims 66-68 recite a neublastin polypeptide comprising an amino acid sequence at least 85%-95% identical to aa 28-140 of SEQ ID NO:2. Thus, the claims are not limited to using proteins with a specific amino acid sequence. Although the specification describes several neubalstin polypeptides on p. 8-13, Applicant fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of neublastin polypeptides comprising homologues with at least 85%, 90% and 95% identical to the aa 28-140 of SEQ ID NO:2. While a generic sequence is provided, there is merely a set of common properties: there is no description of the conserved regions which are critical to the function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the polypeptides with limited homology in the genus from other proteins are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of a neublastin polypeptide might be or a neublastin polypeptide comprising an amino acid sequence at least 85%, 90% and 95% identical to the aa 28-140 of SEQ ID NO:2 might

be. Since the common characteristics/features of all neublastin polypeptides or neublastin polypeptide homologues at least 85%, 90% and 95% identical to the aa 28-140 of SEQ ID NO:2 are unknown, a skilled artisan cannot contemplate the functional correlations of the genus with the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neublastin polypeptide or a neublastin polypeptide comprising an amino acid sequence at least

85%-95% identical to aa 28-140 of SEQ ID NO:2 has not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Obviousness-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28

and 34 of copending Application No. 10/356264 (US20050142098) ('264). Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 encompass a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neubalstin polypeptide. The claims 28 and 34 of '264 encompass a method of treating neuropathic pain and activating the RET receptor in a mammal comprising administering to the mammal an effective amount of the conjugate of different neublastin polypeptides. The instant claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 are unpatentable over claims 28 and 34 of '264 because the method treating neuropathic pain in the instant claims is the same in view of treating neuropathic pain using neubalstin polypeptides. In addition, the working example in the '264 is using NBN113, which is aa 28-140 of SEQ ID NO:2 in the instant application. Furthermore, neublastin executes its activity is through binding of a neublastin dimer to its receptor complex, GFR-α3 and RET receptors. Thus the activation of RET receptor in a mammal is an inherent result of administration of neublastin. While not identical, the claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 of the instant application and the 28 and 34 of '264 encompass a method of treating neuropathic pain overlapping in scope in view of administering neubalstin polypeptides to a subject. Thus, the instant and copending Application claim a non-distinct invention of a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neubalstin polypeptide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-24 of copending Application No. 10/553710. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 encompass a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neubalstin polypeptide. The neuropathic pain in the instant application includes allodynia, hyperalgesic pain, tactile allodynia and neuropathic pain associated with diabetic neuropathy. The claims 15-24 of '710 encompass a method of treating tactile allodynia/thermal hyperalgesia and a method of activating the RET receptor in a mammal comprising administering to the mammal a therapeutically effective amount of the dimer of neublastin polypeptide. The instant claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 are unpatentable over claims 15-24 of '710 because the method of treating neuropathic pain as in the instant claims and the method of '710 encompass a method substantially overlapping in scope in view of treating neuropathic pain using neublastin polypeptides. The monomeric neublastin polypeptide has no activity and the active form of neubalstin polypeptide is a dimer form, which is recited in the '710. In addition, tactile allodynia/thermal hyperalgesia are encompassed in neuropathic pain, which are species anticipating the genus. Furthermore, the signaling mechanism of neublastin is through

the binding of a neublastin dimer to its receptor complex, GFR-α3 and RET receptors, to execute the activity of neublastin. Thus the activation of RET receptor in a mammal is an inherent result of administration of neublastin. While not identical, claims 1, 2, 4, 5, 10-12, 35-37, 57, 66-70 of the instant application and the claim 15-24 of '710 encompass a method substantially overlapping in scope in treating neuropathic pain such as tactile allodynia/thermal hyperalgesia in view of administering neubalstin polypeptides to a subject. Thus, the instant and copending Application claim the same and non-distinct inventions of a method for treating neuropathic pain in a subject comprising administering to a subject a pharmaceutical composition comprising a neubalstin polypeptide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

A search of inventors' names indicates that Applicant files several related applications. It is incumbent on the applicant to inform the office of all related subject matter and to file all related terminal disclaimers. See 37 CFR 1.56, Duty to disclose information material to patentability.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 5, 10-12, 35-37, 57-70 are rejected under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 6734284 (issued on May 11, 2004, priority date Jul 9, 1998, as cited in IDS).

U.S. Patent No. 6734284 ('284) teaches a neublastin polypeptide SEQ ID NO:9, which comprises aa 28-140, 37-140 and 42-140 of instant SEQ ID NO:2 as recited in claims 1, 66-70 (see the sequence search result as set forth below). '284 also teaches using the neublastin polypeptide to treat several neuropathy including injury/trauma-induced neuropathies, chemotherapy-induced neuropathies such as neuropathies induced by delivery of Taxol, drug-induced neuropathies, and diabetic neuropathies as in claims 1, 2, 4, 5, 57, 66-70 (see col. 21 lines 30-57). The neuropathic pain, allodynia, hyperalgesic pain, tactile allodynia and thermal hyperalgesic pain are derived from and accompanied with several pathological conditions including neuropathies as mentioned above as evidenced by Campbell et al. (see p. 78, 1st col., 2nd paragraph to 2nd col. 2nd paragraph, Neuron. 2006. 52: 77-92). The methods of treating drug-induced neuropathies and diabetic neuropathies are incorporated by references as disclosed in US Patent Nos. 5496804 and 5916555. '284 also teaches several delivery routes including intravenous, intraperitoneal and subcutaneous administration as in claims 35-37 (see col. 18, lines 45-67) and different ways to formulate the polypeptide for specific administration routes and time-release (see col.19, lines 33-42).The teachings of '284 meet the limitations of using a neublastin polypeptide or a neubalstin polypeptide

comprising aa 28-140, 37-140, or 42-140 of instant SEQ ID NO:2 or homologues with limited homology of aa 28-140 of instant SEQ ID NO:2 in treating neuropathic pain such as diabetic neuropathy which includes hyperalgesic pain and allodynia. Therefore, Claims 1, 2, 4, 5, 10-12, 35-37, 57-70 are anticipated by U.S. Patent No. 6734284.

Sequence search results disclose as follows:

aa 28-140 of SEQ ID NO:2

```
US-09-662-183A-9
; Sequence 9, Application US/09662183A
; Patent No. 6734284
; GENERAL INFORMATION:
;  APPLICANT: Johansen, Teit E.
;  APPLICANT:  Blom, Nikolaj
;  APPLICANT:  Hansen, Claus
;  TITLE OF INVENTION: No. 6734284el Neurotrophic Factors
;  FILE REFERENCE: 19313-001 DIV
;  CURRENT APPLICATION NUMBER: US/09/662,183A
;  CURRENT FILING DATE:  2000-09-14
;  PRIOR APPLICATION NUMBER: DANISH  1998 00904
;  PRIOR FILING DATE: 1998-07-06
;  PRIOR APPLICATION NUMBER: USSN 60/092,229
;  PRIOR FILING DATE: 1998-07-09
;  PRIOR APPLICATION NUMBER: DANISH  1998 01048
;  PRIOR FILING DATE: 1998-08-19
;  PRIOR APPLICATION NUMBER: USSN 60/097,774
;  PRIOR FILING DATE: 1998-08-25
;  PRIOR APPLICATION NUMBER: DANISH  1998 01260
;  PRIOR FILING DATE: 1998-10-05
;  PRIOR APPLICATION NUMBER: USSN 60/103,908
;  PRIOR FILING DATE: 1998-10-13
;  PRIOR APPLICATION NUMBER: DANISH  1998 01265
;  PRIOR FILING DATE: 1998-10-06
;  PRIOR APPLICATION NUMBER: 09/347,613
;  PRIOR FILING DATE: 2000-07-02
;  NUMBER OF SEQ ID NOS: 43
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 9
;   LENGTH: 220
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-09-662-183A-9

  Query Match             100.0%;  Score 596;  DB 2;  Length 220;
  Best Local Similarity   100.0%;  Pred. No. 3.2e-42;
  Matches  113;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;
```

```
Qy          1 AALALLSSVAEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         28 AALALLSSVAEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSR 87

Qy         61 PAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 113
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         88 PAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 140
```

aa 37-140 of SEQ ID NO:2

```
  Query Match             100.0%;  Score 560;  DB 2;  Length 220;
  Best Local Similarity   100.0%;  Pred. No. 7.1e-39;
  Matches  104;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy          1 AEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSRPAPPPPAPP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         37 AEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSRPAPPPPAPP 96

Qy         61 SALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 104
              ||||||||||||||||||||||||||||||||||||||||||||
Db         97 SALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 140
```

aa 42-140 of SEQ ID NO:2

```
  Query Match             100.0%;  Score 539;  DB 2;  Length 220;
  Best Local Similarity   100.0%;  Pred. No. 7.9e-38;
  Matches   99;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy          1 GSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSRPAPPPPAPPSALPR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         42 GSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSRPAPPPPAPPSALPR 101

Qy         61 GGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 99
              |||||||||||||||||||||||||||||||||||||||
Db        102 GGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 140
```

Claims1, 2, 4, 5, 10-12, 35-37, 57-70 are rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/356264 (US20050142098).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The reasons of the rejection are provided in the section of Obviousness-Type Non-Statutory Double Patenting. In addition, '264 teaches different fragments of SEQ ID NO:2 as in claims 66-70 and conjugating the neublastin polypeptide with a derivative moiety including PEG and aliphatic esters as in claims 10-12 (see p.10, [0080]; p.11 [0091]-[0094]). '264 also teaches treating diabetic neuropathic pain and allodynia and hyperalgesic pain as in claims 2, 35-37, 57 (see p.19;[0198]-[0201]). '264 also teaches administration routes for delivery of neublastin polypeptides as in claims 4,5, 58-65 (see p.21 [0223]-[0225]). Thus, claims 1, 2, 4, 5, 10-12, 35-37, 57-70 are anticipated by copending Application No. 10/356264.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5, 10-12, 35-37 and 57-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6734284 in view of US Patent No. 5414135 (issued May 9, 1995, effective filing date Dec 30, 1991).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

U.S. Patent No. 6734284 teach as set forth above but fails to teach a derivative moiety, polyethylene glycol moiety or aliphatic esters as in claims 10-12.

US Patent No. 5414135 ('135) teaches coupling polyethylene glycol (PEG) as in claims 10-11 can maintain the protein physiologically active and non-immunogenic because polyethylene glycol serves to protect the polypeptide from loss of activity without inducing substantial immunogenic response (see col. 2, lines 30-62). '135 further teaches that proteins can be modified by imino esters, which is one of aliphatic esters as in claim 12 (see col. 2, lines 62-68 and col. 16, example 13). The teachings of '135 provide a motivation and expectation of success in conjugating a protein with a derivative moiety including PEG and aliphatic esters to extend the time of maintaining active concentration of proteins in the body.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify neublastin polypeptides with polyethylene glycol or aliphatic esters. The person of ordinary skill in the art would have been motivated to do so because polyethylene glycol and aliphatic esters have been used to modify polypeptides for pharmaceutical purpose to maintain activity and avoid immunogenicity.

One of ordinary skill in the art would have expected success in modifying neublastin polypeptides with polyethylene glycol or aliphatic esters and using the modified neublastin polypeptides such as aa 28-140 of instant SEQ ID NO:2 in treating neuropathic pain derived from diabetic neuropathy.

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

```
AAY68710
ID   AAY68710 standard; protein; 220 AA.
AC   AAY68710;
DT   05-MAY-2000  (first entry)
DE   A human pre-pro-neublastin neurotrophic factor.
KW   Neurotrophic factor; neublastin; neurodegenerative disease;
     cerebral ischemic neuronal damage; traumatic brain injury;
     peripheral neuropathy; Alzheimer's disease; Huntington's disease;
     Parkinson's disease; Parkinson-Plus syndrome;
     progressive Supranuclear Palsy; Olivopontocerebellar atrophy;
     Shy-Drager Syndrome; Guamanian parkinsonism dementia complex;
     amyotrophic lateral sclerosis; memory impairment; neuronal disorder;
     neuropathy; ischemic stroke; acute brain injury;
     acute spinal cord injury; nervous system tumour; multiple sclerosis;
     neurotoxin exposure; metabolic disease; diabetes; renal dysfunction;
     eye disorder.
OS   Homo sapiens.
FH   Key             Location/Qualifiers
FT   Disulfide-bond  43. .108
     Disulfide-bond  70. .136
     Disulfide-bond  74. .138
     Modified-site   122
                     /note= "glycosylated residue"
PN   WO200001815-A2.
PD   13-JAN-2000.
PF   05-JUL-1999;   99WO-DK000384.
PR   06-JUL-1998;   98DK-00000904.
```

PR 09-JUL-1998; 98US-0092229P.
PR 19-AUG-1998; 98DK-00001048.
PR 25-AUG-1998; 98US-0097774P.
PR 06-OCT-1998; 98DK-00001265.
PR 13-OCT-1998; 98US-0103908P.
PR 02-JUL-1999; 99US-00347613.
PA (NEUR-) NEUROSEARCH AS.
PI Johansen TE, Blom N, Hansen C;
DR WPI; 2000-171013/15.
DR N-PSDB; AAZ60563.
PT New isolated polypeptides, used for treating e.g. neurodegenerative disease or disorder, neuronal damage or neuronal disorder of the peripheral nervous system, the medulla or the spinal cord.
PS Claim 14; Page 97; 106pp; English.
CC The present sequence represents a neurotrophic factor designated neublastin. Neublastin is a member of the glial cell line-derived neurotrophic factor sub-class of the transforming growth factor-beta superfamily of neurotrophic factors. Neublastin exhibits high affinity for the GFR-alpha3-RET receptor complex. The polypeptides can be used for treating a neurodegenerative disease or disorder, cerebral ischemic neuronal damage, traumatic brain injury, peripheral neuropathy, Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson -Plus syndromes, progressive Supranuclear Palsy, Olivopontocerebellar atrophy, Shy-Drager Syndrome, Guamanian parkinsonism dementia complex, amyotrophic lateral sclerosis, memory impairment, or a neuronal disorder of the peripheral nervous system, the medulla or the spinal cord. They can also be used for treating various neuropathies. They can also be used for treating ischemic stroke, acute brain injury, acute spinal cord injury, nervous system tumours, multiple sclerosis, exposure to neurotoxins, metabolic diseases such as diabetes or renal dysfunctions and damage caused by infectious agents, or various disorders in the eye
SQ Sequence 220 AA;

Query Match 100.0%; Score 596; DB 3; Length 220;
Best Local Similarity 100.0%; Pred. No. 5.2e-38;
Matches 113; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 AALALLSSVAEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         28 AALALLSSVAEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSR 87

Qy         61 PAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 113
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         88 PAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 140
```

AAY84583
ID AAY84583 standard; protein; 220 AA.
XX
AC AAY84583;
XX
DT 25-JUL-2000 (first entry)
XX

DE Amino acid sequence of a human pre-pro-artemin polypeptide.
XX
KW Human; artemin; growth factor; neurotrophic factor; trophic support;
KW neuron; trigeminal ganglion neuron; nodose ganglion neuron;
KW superior cervical ganglion neuron; midbrain neuron; Alzheimer's disease;
KW peripheral neuropathy; amylotrophic lateral sclerosis; ischemic stroke;
KW Parkinson's disease; Huntington's disease; acute brain injury;
KW acute spinal cord injury; nervous system tumour; blastoma;
KW multiple sclerosis; infection; enteric disease; idiopathic constipation;
KW Parkinson's disease; small cell lung carcinoma.
XX
OS Homo sapiens.
XX
PN WO200018799-A1.
XX
PD 06-APR-2000.
XX
PF 29-SEP-1999; 99WO-US022604.
XX
PR 29-SEP-1998; 98US-00163283.
PR 12-NOV-1998; 98US-0108148P.
PR 22-DEC-1998; 98US-00218698.
XX
PA (UNIW) UNIV WASHINGTON.
XX
PI Milbrandt JD, Baloh RH;
XX
DR WPI; 2000-293109/25.
DR N-PSDB; AAA12540.
XX
PT Isolated artemin growth factor proteins and the nucleic acids that encode
PT them, useful for treating a range of degenerative neuronal disorders such
PT as Parkinson's disease and Huntington's disease.
XX
PS Claim 5; Fig 1B; 96pp; English.
XX
CC The present sequence represents a pre-pro- artemin growth factor protein.
CC Artemin is a neurotrophic factor that belongs to the GDNF (glial cell
CC line-derived neurotrophic factor)/neurturin/persephin family of growth
CC factors and promotes differentiation, maintains mature phenotype and
CC provides trophic support, promoting growth and survival of neurons.
CC Artemin promotes the survival of trigeminal ganglion neurons, nodose
CC ganglion neurons, superior cervical ganglion neurons and tyrosine-
CC hydroxylase-expressing dopaminergic ventral midbrain neurons. Artemin is
CC the only member of the GDNF family that binds to GFR-alpha (growth factor
CC receptor-alpha) and activates the GFR-alpha3/RET (Ret protein- tyrosine
CC kinase) receptor complex and additionally, like GDNF and neurturin,
CC artemin also binds to and activates GFRalpha1/RET. Artemin polypeptides
CC and polynucleotides are administered to treat peripheral neuropathy,
CC amylotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease,
CC Huntington's disease, ischemic stroke, acute brain injury, acute spinal
CC cord injury, a nervous system tumour (e.g. blastomas), multiple
CC sclerosis, infection or enteric disease (e.g. idiopathic constipation or
CC constipation associated with Parkinson's disease, spinal cord injury or

```
CC   use of opiate pain killers). They may also be used to treat a patient
CC   suffering from small cell lung carcinoma
XX
SQ   Sequence 220 AA;

  Query Match             100.0%;  Score 596;  DB 3;  Length 220;
  Best Local Similarity   100.0%;  Pred. No. 5.2e-38;
  Matches  113;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 AALALLSSVAEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         28 AALALLSSVAEASLGSAPRSPAPREGPPPVLASPAGHLPGGRTARWCSGRARRPPPQPSR 87

Qy         61 PAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 113
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         88 PAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHR 140
```

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
December 12, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

PTO-1449 paper no/mail date 11/27/06